REMARKS

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

I. Restriction requirement/election

Election, with traverse, of the claims of Group II (encompassing claims 46, 48-49, 51, and 53-60), drawn to antibodies to the polypeptide of SEQ ID NO:1, compositions thereof, and methods of making the antibodies, is acknowledged.

Claims directed to methods of using the antibodies for diagnosing disease (i.e., claim 47), for detecting polypeptides specifically bound by the antibodies (i.e., claim 61), and for purifying polypeptides specifically bound by the antibodies (i.e., claim 62), could and should be examined together with the product claims from which they depend, per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products. Applicants presume that these method claims will be rejoined, upon determining allowability of the product claims from which they depend.

II. Priority

As suggested by the Examiner, the first sentence of the application has been amended to update the status of the priority documents.

III. Drawings

Figure 2C was objected to because the left margin of the drawing is unacceptable (Office Action, October 21, 2002; Notice of Draftsperson's Patent Drawing Review). Corrected formal drawings are submitted herewith. Therefore, withdrawal of this objection is requested.

IV. Written description rejection under 35 U.S.C. § 112, first paragraph

Claims 46, 48-49, 51, and 53-60 were rejected under 35 U.S.C. § 112, first paragraph, as being based on a specification which allegedly fails to reasonably convey to one of skill in the art that the Applicants had possession of the claimed invention at the time the application was filed. The Office Action states that "the antibodies encompassed are directed not only to a polypeptide having an amino acid sequence of SEQ ID NO:1, but also to variants of said polypeptide . . . which include polypeptides with no recited functional limitations" (Office Action, October 21, 2002; page 4) and asserts that "[t]he instant disclosure of an antibody to SEQ ID NO:1 does not adequately describe the scope of the claimed genus" (Office Action, page 5). This rejection is traversed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*
> *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every

nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The specification provides an adequate written description of the claimed antibodies which specifically bind to the recited "variants" and "fragments" of SEQ ID NO:1.

The subject matter encompassed by claims 46, 48-49, 51, and 53-60 is either disclosed by the specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of independent claim 46 recites polypeptides comprising "a polypeptide having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein the polypeptide has nucleotide pyrophosphohydrolase activity." Furthermore, the "fragment" language of independent claim 46 recites polypeptides comprising "a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the fragment has nucleotide pyrophosphohydrolase activity," and polypeptides comprising "an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1." The polypeptide sequence of SEQ ID NO:1 is explicitly disclosed in the specification. See, for example, the Sequence Listing and Figures 1A, 1B, 1C, 1D, 1E, 1F, 1G, 1H, 1I, 1J, 1K, 2A, 2B, and 2C. Variants of SEQ ID NO:1 are described in the specification at, for example, page 3, lines 20-22; page 8, lines 16-25; page 8, line 30 to page 9, line 4; page 11, lines 13-15; page 13, lines 1-3; page 15, lines 4-5 and 16-24; page 17, lines 1-5; and page 21, lines 20-22; and fragments of SEQ ID NO:1 are described at, for example, page 3, lines 20-22 and 27-29; page 4, lines 24-29; page 8, lines 26-30; page 9, lines 15-28; page 10, lines 7-11; page 18, lines 6-11; page 21, lines 11-15; page 30, lines 23-25; page 31, lines 7-13; page 45, lines 28-30; page 55, lines 13-14; and page 55, line 28 to page 56, line 12. In addition, a specific assay to measure nucleotide pyrophosphohydrolase activity is disclosed in the specification at, for example, page 55, lines 22-26.

One of ordinary skill in the art would recognize polypeptide sequences which are variants that are at least 90% identical to SEQ ID NO:1. Given any naturally occurring polypeptide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:1. It

would also be routine to determine whether such a variant had nucleotide pyrophosphohydrolase activity, using the disclosed nucleotide pyrophosphohydrolase assay. Accordingly, the specification provides an adequate written description of the claimed antibodies which specifically bind to the recited polypeptide variants of SEQ ID NO:1.

One of ordinary skill in the art would recognize polypeptide sequences which are fragments of SEQ ID NO:1. The amino acid sequence of SEQ ID NO:1 provides the necessary framework for the recited fragments - to recite every possible fragment would needlessly clutter the application. It would be routine for one of skill in the art to determine whether any particular fragment of SEQ ID NO:1 had nucleotide pyrophosphohydrolase activity, using the disclosed nucleotide pyrophosphohydrolase assay. Likewise, it would be routine for one of skill in the art to determine whether any particular fragment of SEQ ID NO:1 had immunogenic activity, based on the methods recited in the specification at, for example, page 9, lines 13-29; page 30, line 15 to page 32, line 15; and page 55, line 28 to page 56, line 12. Accordingly, the specification provides an adequate written description of the claimed antibodies which specifically bind to the recited polypeptide fragments of SEQ ID NO:1.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define the polypeptides bound by the claimed antibodies in terms of chemical structure, rather than functional characteristics. For example, the language of independent claim 46 recites chemical structure to define the claimed genus:

> 46. An isolated antibody which specifically binds to a polypeptide comprising a polypeptide selected from the group consisting of:
> a) a polypeptide having the amino acid sequence of SEQ ID NO:1,
> b) a polypeptide having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein the

polypeptide has nucleotide pyrophosphohydrolase activity;

c) a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the fragment has nucleotide pyrophosphohydrolase activity, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1.

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides specifically bound by the claimed antibodies. The polypeptides defined by the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that, rather than being a large variable genus, the genus of polypeptides recited by the claims is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

The present application is directed, *inter alia*, to polypeptides which are nucleotide pyrophosphohydrolases including polypeptides which are nucleotide pyrophosphohydrolases related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as nucleotide pyrophosphohydrolases and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "variant language" of the present claims recites a polypeptide comprising "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 1156 amino acid residues). This variation is far less than that of all potential nucleotide pyrophosphohydrolases related to SEQ ID NO:1, i.e., those nucleotide pyrophosphohydrolases having as little as 30% identity over at least 150 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. § 112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those cases was based on the state of the art at essentially the "dark ages" of recombinant DNA technology.

The present application has a priority date of December 22, 1997. Much has happened in the development of recombinant DNA technology in the 20 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed antibodies which specifically bind the recited polypeptide variants and fragments at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Office Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims reciting nucleic acids and proteins. In addition, the genus of polypeptides recited by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the reasons set forth above, the specification provides an adequate written description of the claimed antibodies which specifically bind to the recited polypeptide "variants" and "fragments," and this rejection should be withdrawn.

V. Enablement rejection under 35 U.S.C. § 112, first paragraph

Claims 46, 48-49, 51, and 53-60 were rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter of the invention in such a way as to enable one of skill in the art to make and/or use antibodies which specifically bind to the recited "variants" and "fragments" of SEQ ID NO:1 (Office Action, October 21, 2002; pages 5-7). In particular, the Office Action has asserted that "it would require undue experimentation for one of skill in the art to predict how to make and use antibodies which specifically bind to the recited fragments [of] a polypeptide having an amino acid sequence of SEQ ID NO:1 or to polypeptides with 90% identity to a polypeptide having an amino acid sequence of SEQ ID NO:1, without further guidance and direction from the specification regarding the functional activities of the polypeptides" (Office Action, page 6). Such, however, is not the case.

The specification discloses methods to make antibodies which specifically bind to a polypeptide having **any** particular amino acid sequence (e.g., at page 30, line 15 to page 32, line 15; and page 55,

line 28 to page 56, line 12). Given the information provided by SEQ ID NO:1 (the amino acid sequence of NTPPH-2), one of skill in the art would be able to routinely obtain antibodies which specifically bind to any of the recited variants and fragments of SEQ ID NO:1, including a polypeptide comprising "a polypeptide having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1," a polypeptide comprising "a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1," and a polypeptide comprising "an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1." For example, an animal could be immunized with any of the recited variants and fragments of SEQ ID NO:1, antibodies could be isolated from the animal, and the antibodies could be screened to identify antibodies which specifically bind to the polypeptide.

Likewise, the specification discloses methods to use antibodies which specifically bind to a polypeptide having **any** particular amino acid sequence in, for example, the purification of such polypeptides (e.g., at page 56, lines 14-24), the detection and/or measurement of such polypeptides (e.g., at page 26, line 25 to page 27, line 3; and page 38, line 14 to page 39, line 5), and the competitive screening of drug candidates (e.g., at page 46, lines 27-30). Given the information provided by SEQ ID NO:1 (the amino acid sequence of NTPPH-2), one of skill in the art would be able to routinely use antibodies which specifically bind to any of the recited variants and fragments of SEQ ID NO:1, including a polypeptide comprising "a polypeptide having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1," a polypeptide comprising "a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1," and a polypeptide comprising "an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1." For example, an antibody which specifically binds to any of the recited variants and fragments of SEQ ID NO:1 could be coupled to an activated chromatographic resin, and this resin could then be used in an immunoaffinity column to purify the polypeptide.

In support of this rejection, the Office Action states that "the specification does not appear to disclose the sequence of any said polypeptides comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1" (Office Action, October 21, 2002; page 6). Furthermore, the Office Action asserts that "[t]he specification does not appear to disclose or exemplify any said biologically active or immunogenic fragments of a polypeptide having an amino acid sequence

of SEQ ID NO:1" (Office Action, page 6). The Office Action is incorrect in asserting that the recited polypeptide variants and fragments which are specifically bound by the claimed antibodies are not disclosed by the specification. Variants of SEQ ID NO:1 are disclosed in the specification at, for example, page 3, lines 20-22; page 8, lines 16-25; page 8, line 30 to page 9, line 4; page 15, lines 16-24; page 17, lines 1-5; and page 21, lines 20-22. Fragments of SEQ ID NO:1 are disclosed in the specification at, for example, page 3, lines 20-22 and 27-29; page 8, lines 26-30; page 9, lines 15-28; page 10, lines 7-11; page 30, lines 23-25; page 31, lines 7-13; and page 55, line 28 to page 56, line 12. In addition, an assay to measure a biological activity recited in the claims, nucleotide pyrophosphohydrolase activity, is disclosed in the specification at, for example, page 55, lines 22-26. Therefore, the recited polypeptide variants and fragments are fully disclosed in the specification. Furthermore, antibodies which specifically bind to NTPPH-2, and variants and fragments thereof, are disclosed in the specification at, for example, page 4, lines 27-29; page 9, lines 13-21; and page 31, lines 7-13.

The Office Action is incorrect in asserting that "undue experimentation" would be required to make and use the claimed antibodies. Antibodies which specifically bind to a polypeptide can be made as long as that polypeptide, or fragments thereof, are available; there is no restriction on the amino acid sequence of polypeptides that can be used to make antibodies. Since a polypeptide having **any** amino acid sequence (including any amino acid sequence that is 90% identical to SEQ ID NO:1, any naturally occurring amino acid sequence that is 90% identical to SEQ ID NO:1, and any fragment of SEQ ID NO:1) can be used to make antibodies using the methods disclosed in the specification, it is not necessary to identify particular naturally occurring amino acid sequences that are 90% identical to SEQ ID NO:1, or particular fragments of SEQ ID NO:1, that could be used in this manner.

The Office Action attempts to provide further support for the assertion that undue experimentation would be required to make and use the claimed antibodies by citing Sugie et al. (Proc. Natl. Acad. Sci. USA, 1997, 94:5278-5283). This reference teaches that human glycosylation-inhibiting factor differs from human macrophage migration inhibitory factor by one amino acid residue, and yet these proteins do not share all of their biological functions (Office Action, October 21, 2002; page 6). The Office Action continues this argument by stating that "[w]ithout knowing the function of the polypeptides related to a polypeptide comprising an amino acid sequence comprising SEQ ID

NO:1, it would require undue experimentation for one of skill to predict the function of antibodies which specifically binds to said polypeptides" (Office Action, October 21, 2002; pages 6-7). This is incorrect. No undue experimentation would be required because it is a trivial matter to "predict the function of antibodies" which specifically bind to the recited polypeptides. The "function" of such antibodies is to **specifically bind to** the recited polypeptides, and a skilled artisan would recognize this immediately.

Furthermore, the Office Action has ignored the guidance provided by the claims themselves and the specification. For example, the claimed antibodies include antibodies which specifically bind to a polypeptide comprising "a polypeptide having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein the polypeptide has nucleotide pyrophosphohydrolase activity," and to a polypeptide comprising "a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the fragment has nucleotide pyrophosphohydrolase activity." An assay to measure nucleotide pyrophosphohydrolase activity is disclosed in the specification at, for example, page 55, lines 22-26. One of ordinary skill in the art could routinely use the disclosed assay to identify polypeptide variants and fragments recited by the claims, and could routinely make and/or use antibodies which specifically bind to these polypeptide variants and fragments. Likewise, a skilled artisan could routinely determine if a fragment was immunogenic by attempting to raise antibodies to that fragment and then determining if any antibodies so raised could specifically bind to that fragment. Contrary to the Office Action's assertions, no undue experimentation would be required.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Office Action has failed to provide any **reasons** why one would doubt that the guidance provided by the present specification would enable one to make and use the claimed antibodies which specifically bind to the recited variants and fragments of SEQ ID NO:1. Hence, a *prima facie* case for non-enablement has not been established with respect to the claimed antibodies which specifically bind to the recited variants and fragments of SEQ ID NO:1.

For at least the above reasons, withdrawal of this rejection is requested.

VI. Rejections under 35 U.S.C. § 112, second paragraph

Claims 46, 48-49, 51, and 53-60 were rejected under 35 U.S.C. § 112, second paragraph, based on the allegation that these claims depend on canceled claim 45 (Office Action, October 21, 2002; page 7). Applicants respectfully point out that, although claim 45 has been withdrawn from consideration, it has not been canceled (see, for example, page 2 of the Office Action).

Claim 46 has been amended such that it is not dependent on claim 45. It is believed that claim 46, and claims 48-49, 51, and 53-60, which are dependent on claim 46, recite patentable subject matter. Therefore, withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, is requested.

Claims 46, 48-49, 51, and 53-60 were further rejected under 35 U.S.C. § 112, second paragraph, based on the allegation that the recitation of "at least 90% identical" is indefinite. The Office Action asserts that "the algorithm used to define identity is not disclosed in the specification," and that "[i]t is not clear how an amino acid sequence can have homology to another amino acid sequence" (Office Action, October 21, 2002; page 7). This rejection is traversed.

Under the second paragraph of 35 U.S.C. § 112, the standard for "definiteness" is that the claims define patentable subject matter with a **reasonable** degree of precision and particularity. See *In re Miller*, 169 USPQ 597, 599 (CCPA 1971); *In re Moore*, 169 USPQ 236, 238 (CCPA 1971). See also M.P.E.P. § 706.03(d). In this regard, the Supreme Court has indicated that the primary purpose of claim language is to give "fair" notice of what would constitute the infringement of a claim. See *United Carbon Co. v. Binny & Smith Co.*, 317 U.S. 228, 55 USPQ 381 (1942). In other

words, the basic purpose of 35 U.S.C. § 112, second paragraph is to require a claim to reasonably apprise those skilled in the art of the scope of the invention defined by that claim and give fair notice of what constitutes infringement of the claim. See *Antonius v. Pro Group Inc.*, 217 USPQ 875, 877 (6th Cir.1983). The present claims meet the legal standards required by 35 U.S.C. § 112, second paragraph.

One of ordinary skill in the art would understand the meaning of the term "at least 90% identical" when this term is used for defining the structure of an amino acid sequence in relation to a reference amino acid sequence, as in the claims at issue. The Office Action recognizes this in stating that the term "identity" is "defined in the specification on page 11, by stating that the term identity may substitute for the term homology and **refers to a degree of complementarity**" (Office Action, October 21, 2002; page 7; emphasis added). However, the Office Action errs in requiring an explicit disclosure of the algorithm used to calculate percent identity. A skilled artisan would reasonably understand that the percent identity of two amino acid sequences can be calculated using basic mathematics. For example, to arrive at the percent identity, a subject sequence and a reference sequence are compared, the number of amino acids which are identical in these sequences is summed up, and the result is divided by the total number of amino acids in the reference sequence. Therefore, the claims are definite in their recitation of amino acid sequences which are "at least 90% identical" to the amino acid sequence of SEQ ID NO:1.

For at least the above reasons, withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, is requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at (650) 621-8581.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

Respectfully submitted,

INCYTE GENOMICS, INC.

Date: Jan. 17, 2003

Terence P. Lo, Ph.D.
Limited Recognition (37 C.F.R. § 10.9(b)) attached
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

The paragraph immediately following the title has been amended as follows:

This application is a **DIVISIONAL** of U.S. application Serial No. 09/429,516, filed October 28, 1999, which issued on June 26, 2001 as U.S. Patent No. 6,251,389, entitled HUMAN NUCLEOTIDE PYROPHOSPHOHYDROLASE-2, which is a divisional application of U.S. application Serial No. 08/996,083, filed December 22, 1997, which issued on September 26, 2000 as U.S. Patent No. 6,124,095, entitled HUMAN NUCLEOTIDE PYROPHOSPHOHYDROLASE-2, the contents all of which are hereby incorporated by reference.

IN THE CLAIMS

Claims 50, 52, and 63-64 have been canceled, without prejudice or disclaimer.

Claims 46-47, 51, and 54 have been amended as follows:

46. (Once Amended) An isolated antibody which specifically binds to a polypeptide comprising a polypeptide selected from the group consisting of [claim 45] :

a) a polypeptide having the amino acid sequence of SEQ ID NO:1,

b) a polypeptide having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein the polypeptide has nucleotide pyrophosphohydrolase activity,

c) a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the fragment has nucleotide pyrophosphohydrolase activity, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1.

47. (Once Amended) A method for a diagnostic test for a condition or disease associated with the expression of human nucleotide pyrophosphohydrolase-2 in a biological sample, the method comprising:

a) combining the biological sample with an antibody of claim 46, under conditions suitable for the antibody to bind the polypeptide and form an antibody:polypeptide complex, and

b) detecting the complex, wherein the presence of the complex correlates with the presence of the polypeptide in the biological sample.

51. (Once Amended) A composition of claim 49, [wherein the antibody is labeled] further comprising a label.

54. (Once Amended) [An] A polyclonal antibody produced by a method of claim 53.

New claims 65-68 have been added as follows:

65. (New) An isolated antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1.

66. (New) An isolated antibody of claim 46, which specifically binds to a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein the polypeptide has nucleotide pyrophosphohydrolase activity.

67. (New) An isolated antibody of claim 46, which specifically binds to a fragment of a polypeptide, wherein the polypeptide consists of the amino acid sequence of SEQ ID NO:1, and wherein the fragment has nucleotide pyrophosphohydrolase activity.

68. (New) An isolated antibody of claim 46, which specifically binds to an immunogenic fragment of a polypeptide, wherein the polypeptide consists of the amino acid sequence of SEQ ID NO:1.